IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences

In re Patent Application of

IBRAHIM et al

Serial No. 10/049,379

Filed: February 12, 2002

Atty Dkt. 2590-35
C# M#

TC/A.U.: 1615

Examiner: Robert M. Joynes

Date: November 17, 2004

Title: PHARMACEUTICALLY STABLE OXALIPLATINUM PREPARATION FOR PARENTERAL ADMINISTRATION

IFW

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

☐ **Correspondence Address Indication Form Attached.**

☐ **NOTICE OF APPEAL**
Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner twice/finally rejecting ($340.00) applicant's claim(s). $

☒ An appeal **BRIEF** is attached in the pending appeal of the above-identified application ($ 340.00) $ 340.00

☐ Credit for fees paid in prior appeal without decision on merits -$ ( )

☐ A reply brief is attached in triplicate under Rule 41.41 **(no fee)**

☐ Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) (**$110.00/1 month**; $430.00/2 months; **$980.00/3 months**; $1530.00/4 months) $

SUBTOTAL $ 340.00

☐ Applicant claims "Small entity" status, enter ½ of subtotal and subtract -$( )
☐ "Small entity" statement attached.

SUBTOTAL $ 340.00

Less month extension previously paid on -$(0.00)

TOTAL FEE ENCLOSED $ 340.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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Signature: D Byers

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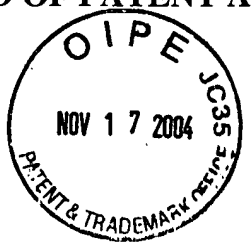
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES



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* *

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Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the Examiner, which is an anticipated, but not yet received, Advisory Action in response to Applicant's Amendment After Final Rejection dated September 17, 2004.

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(I) REAL PARTY IN INTEREST

The real party in interest is the owner of the subject application, namely, DEBIOPHARM S.A., a corporation of the country of Switzerland.

(II) RELATED APPEALS AND INTERFERENCES

The appellant, the undersigned, and the assignee are not aware of any related appeals, interferences, or judicial proceedings (past or present), which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(III) STATUS OF CLAIMS

Claims 1-11 and 15-17 are pending and have been rejected. All of these claims are the subject of this appeal, but are not grouped as a whole. During prosecution, claims 12-14 were cancelled without prejudice. No claims have been substantively allowed.

(IV) STATUS OF AMENDMENTS

Since the date of the Final Rejection of June 17, 2004, the following events have occurred:

An Interview was held with the Examiner on August 11, 2004.

The Examiner issued an Interview Summary on August 11, 2004.

Applicant's counsel filed an Interview Summary Statement on August 13, 2004.

Applicant filed an Amendment After Final Rejection on September 17, 2004.

Applicant's counsel left telephone messages with the Examiner (Mr. Joynes) on November 8 and 11, 2004, inquiring about the status of the case.

Applicant's counsel contacted the Examiner's supervisor (Mr. Page) on November 12, 2004, inquiring about the status of the case and was informed that Examiner Joynes was no longer with the U.S. Patent and Trademark Office.

The Examiner's supervisor kindly reviewed the case and telephoned applicant's counsel on November 15, 2004, with some suggested claim revisions for the case.

As relayed via voice mail by applicant's counsel to the Examiner's supervisor on November 17, 2004, the applicant respectfully did not concur with the suggested claim revisions.

During the voice mail message of November 17, 2004, applicant's counsel respectfully requested issuance of an Advisory Action on November 17, 2004 (the date this Appeal Brief was due), indicating entry of applicant's Amendment After Final Rejection dated September 17, 2004, because the Amendment placed the case in better condition for appeal.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

The invention of the claims relates to an oxaliplatinum stable pharmaceutical preparation comprising oxaliplatinum contained in a solvent at a concentration of at least 7 mg/ml and wherein the solvent comprises a sufficient quantity of hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol. Applicants have surprisingly discovered that the claimed critical concentration (at least 7 mg/ml) in a solvent that comprises a sufficient quantity of a hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol provides a stable, concentrated pharmaceutical preparation. In other words, applicants have surprisingly discovered that oxaliplatinum at this level of concentration and in this solvent has an unexpected stability in a wide range of utilization temperatures. See, for example, the explanation of these discoveries on pages 2-4 of the application. As noted in the specification, this novel and non-obvious preparation is clear, colorless and free of precipitate and remains in this stable form for an extended duration of time.

Appealed Claims

Claim 1 concerns a stable pharmaceutical preparation comprising oxaliplatinum contained in a solvent at a concentration of at least 7 mg/ml and wherein the solvent comprises a sufficient quantity of hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol. See, e.g., application at page 3, lines 22-26.

Claim 2 depends from claim 1 and requires that the oxaliplatinum is contained in a solution in the solvent at a concentration of at least 9 mg/ml and wherein 1 ml of the solvent comprises at least 100 mg of one or several of the hydroxylated derivatives. See, e.g., application at page 4, lines 29-30.

Claim 3 depends from claim 2 and requires that the solvent further comprises water. See, e.g., application at page 5, line 4.

Claim 4 depends from claim 3 and requires that the oxaliplatinum is contained in a solution in the solvent at a concentration between about 10 mg/ml and about 15 mg/ml. See, e.g., application at page 5, lines 6-7.

Claim 5 depends from claim 1 and requires that the pharmaceutical preparation is packed in an appropriate container for parenteral administration. See, e.g., application at page 6, lines 1-4.

Claim 6 depends from claim 5 and requires that the container be a multidoses flask. Claim 15 depends from claim 1 and requires a mutlidoses flask. See, e.g., application at page 6, lines 1-4.

Claim 7 depends from claim 5 and requires that the container is a prefilled syringe. Claim 16 depends from claim 1 and requires a prefilled syringe. See, e.g., application at page 6, lines 1-4.

Claim 8 depends from claim 5 and requires that the container is a soft perfusion bag. Claim 17 depends from claim 1 and requires a soft perfusion bag. See, e.g., application at page 6, lines 1-4.

Claim 9 depends from claim 5 and requires that the container is an ampoule. See, e.g., application at page 6, lines 1-4.

Claim 10 concerns a method for the preparation of a stable pharmaceutical preparation according to claim 1 that comprises a step of mixing oxaliplatinum with a solvent comprising a sufficient quantity of at least one hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol. See, e.g., application at page 7, lines 1-5.

Claim 11 depends from claim 10 and requires a method comprising the following steps:

a) putting in contact, at a temperature less than 80°C, a quantity of oxaliplatinum with a sufficient quantity of the solvent in order to obtain an oxaliplatinum concentration of at least 7 mg/ml;

b) establishing the mixture obtained in step a) at a temperature between 15-30°C;

c) submitting the mixture obtained in step b) to an aseptic filtration; and

d) conserving, in an adapted container for a parenteral administration, the mixture obtained in step c) at a temperature between 2-30°C.

See, e.g., application at page 7, lines 6-15.

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1-11 and 15-17 were properly rejected under 35 U.S.C. §103(a) as being unpatentable over Ibrahim et al. (U.S. Patent No. 5716988) in combination with Schilpalius (U.S. Patent No. 5897871) or Blackshear et al. (U.S. Patent No. 4439181).

The claims are being separately argued on appeal in the following groupings: claim 1, claim 2, claim 3, claim 4, claims 5-9 and 15-17, claim 10, and claim 11.

(VII) ARGUMENT

Claims 1-11 and 15-17 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Ibrahim (U.S. Patent No. 5,716,988) in combination with Schilpalius (U.S. Patent No. 5,897,871) or Blackshear (U.S. Patent No. 4,439,181). *See* Office Action of June 17, 2004, at page 2. Applicant respectfully requests the reversal of the rejection for the following reasons.

At the outset, applicant reconfirms for the record that the preamble of claim 1 is considered a limiting preamble that assists in distinguishing the claimed invention from the cited art. All claims depend from claim 1. However, the claims are being separately argued on appeal in the following groupings: claim 1, claim 2, claim 3, claim 4, claims 5-9 and 15-17, claim 10, and claim 11.

The present invention concerns a specific oxaliplatinum stable pharmaceutical preparation comprising oxaliplatinum contained in a solvent at a concentration of at least 7 mg/ml and wherein the solvent comprises a sufficient quantity of hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol. As noted in the application, the inventors have surprisingly discovered that the claimed critical concentration (at least 7 mg/ml) in a solvent that comprises a sufficient quantity of a hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol provides a stable, concentrated pharmaceutical preparation. In other words, the inventors have surprisingly discovered that oxaliplatinum at this level of concentration and in this solvent has an unexpected stability in a wide range of utilization temperatures. See, for example, the explanation of these discoveries on pages 2, 3 and 4 of the application. As noted in the specification, this novel and non-obvious preparation is clear, colorless and free of precipitate and remains in this stable form for an extended duration of time.

Neither the primary reference nor some combination with the secondary references discloses or suggests the claimed composition, concentration or solvents for such a pharmaceutical preparation. Indeed, and as correctly noted in the Office Action dated September 26, 2003 (page 4, first full paragraph), the primary reference Ibrahim "does not expressly teach the exact concentration for the oxaliplatinum nor does the reference teach other solvents for the solution." This clear and unequivocal statement of the deficiencies of the primary reference -- as correctly set forth in the Office Action -- highlights the novelty and nonobviousness of the claimed invention.

Moreover, the Ibrahim reference actually teaches away from the claimed invention. In particular, Ibrahim describes a pharmaceutical preparation of oxaliplatinum wherein the oxaliplatinum is dissolved in water at a concentration in the range from 1 to 5 mg/ml, and **preferably** at a concentration of 2 mg/ml. See, column 2, lines 9-13 and lines 2-22 of Ibrahim. Thus, the primary reference Ibrahim teaches away from the claimed invention. To say otherwise would run contrary to the express teachings of Ibrahim and would merely confirm the improper hindsight use of the subject application.

The secondary references of Schilpalius and Blackshear do not overcome the deficiencies of the primary reference. Schilpalius does not describe or suggest any composition or method leading to a pharmaceutically stable preparation of oxaliplatinum as claimed in claim 1 of the subject application. This reference merely describes a method for obtaining a beta-carotene composition in an emulsified form. See, for example, column 5, lines 41-49 and column 5, line 53 to column 6, line 11 of Schilpalius. This disclosure is completely unlike the claimed invention. Moreover, there is no motivation or suggestion in either the primary reference or this secondary reference to combine these two references and end up with the claimed invention. Indeed, as noted above, to modify the primary reference in some fashion and arrive at the

claimed invention would run contrary to the express teachings of the primary reference and merely confirm the improper use of hindsight to formulate an obviousness rejection.

Nor does the Blackshear secondary reference overcome the deficiencies of either the primary reference or the other secondary reference. Blackshear does not describe or suggest any composition or method leading to a pharmaceutically stable preparation of oxaliplatinum as claimed in claim 1 of the subject application. Blackshear merely describes a method for maintaining fluidity of protein solutions, for example, insulin solution. Again, like Schlipalius, there is no motivation for a person skilled in the art to combine the oxaliplatinum composition of Ibrahim of from 1 to 5 mg/ml with the Blackshear composition or components thereof and arrive at the claimed invention – i.e., an oxaliplatinum stable pharmaceutical preparation at a concentration of at least 7 mg/ml and in a solvent that comprises a sufficient quantity of hydroxylated derivative selected from 1,2-propanediol, glycerol, maltitol, saccharose and inositol. Again, only improper hindsight would provide for the combination of Blackshear with the primary reference to render the claimed invention obvious -- and, moreover, it would run counter to the express and preferred teachings of the primary reference (using a low concentration and a different solvent).

For the foregoing reasons, claim 1 is patentable over the cited references.

With respect to claim 2, and in addition to the foregoing facts, there is no disclosure or suggestion in the three cited references to prepare a stable pharmaceutical composition wherein the oxaliplatinum is contained in a solution in the solvent at a concentration of at least 9 mg/ml and wherein 1 ml of the solvent comprises at least 100 mg of one or several of the hydroxylated derivatives. In fact, the references teach further away from this claimed invention. As a result, claim 2 is patentable over the cited references.

With respect to claim 3, and in addition to the foregoing facts, there is no disclosure or suggestion in the three cited references to prepare the stable pharmaceutical composition of claim 2 and wherein the solvent further comprises water. Again, the references teach away from this invention because if water is used, then one would assume from the teaching of the primary reference that a stable composition would not result when the oxaliplatinum concentration is at least 9 mg/ml. As a result, claim 3 is patentable over the cited references.

With respect to claim 4, and in addition to the foregoing facts, there is no disclosure or suggestion in the three cited references to prepare the stable pharmaceutical composition of claim 4 wherein the oxaliplatinum concentration is between 10 and 15 mg/ml. This concentration is 100 to 200% greater than the maximum concentration taught in the primary reference – and 500 to 750% greater than the suggested concentration in the primary reference – and aside from the fact that the solvent system is different. As a result, claim 4 is patentable over the cited references.

With respect to claims 5-9 and 15-17, and in addition to the foregoing facts, there is no disclosure or suggestion in the three cited references to prepare the claimed stable pharmaceutical composition and package or place them in the specific devices covered by these claims and that would maintain the compositions stability. Again, the cited references teach away from the claimed composition and its packaging in any form. As a result, claims 5-9 and 15-17 are patentable over the cited references.

With respect to claim 10, and in addition to the foregoing facts, there is no disclosure or suggestion in the three cited references to prepare the claimed stable pharmaceutical composition containing oxaliplatinum in a solvent at a concentration of at least 7 mg/ml and mixing oxaliplatinum with a solvent comprising a sufficient quantity of at least one hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol. As noted

above, and in the Office Action of September 2003, the primary reference does not teach the claimed concentration nor the claimed solvents. Thus, it provides no teaching or suggestion of the claimed method. The secondary references are even further removed from the claimed invention and provide no suggestion to utilize the claimed method. As a result, claim 10 is patentable over the cited references.

With respect to claim 11, and in addition to the foregoing facts, it depends from claim 10 and includes various temperature and processing conditions that are no where found in the cited references. As a result, claim 11 is patentable over the cited references.

CONCLUSION

In conclusion, it is believed that the application is in clear condition for allowance; therefore, early reversal of the Final Rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

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By: _____

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(VIII) CLAIMS APPENDIX

1. Oxaliplatinum stable pharmaceutical preparation for parenteral administration, characterized in that the oxaliplatinum is contained in a solution in a solvent at a concentration of at least 7 mg/ml and in that said solvent comprises a sufficient quantity of a hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol.
2. Pharmaceutical preparation according to claim 1, characterized in that the oxaliplatinum is contained in a solution in said solvent at a concentration of at least 9 mg/ml and in that 1 ml of said solvent comprises at least 100 mg of one or several of said hydroxylated derivatives.
3. Pharmaceutical preparation according to claim 2, characterized in that said solvent further comprises water.
4. Pharmaceutical preparation according to claim 3, characterized in that the oxaliplatinum is contained in a solution in said solvent at a concentration comprised between about 10 mg/ml and about 15 mg/ml.
5. Pharmaceutical preparation according to claim 1, characterized in that it is packed in an appropriate container for parenteral administration.
6. Pharmaceutical preparation according to claim 5, characterized in that said container is a multidoses flask.
7. Pharmaceutical preparation according to claim 5, characterized in that said container is a prefilled syringe.
8. Pharmaceutical preparation according to claim 5, characterized in that said container is a soft perfusion bag.

9. Pharmaceutical preparation according to claim 5, characterized in that said container is an ampoule.

10. Method for the preparation of a pharmaceutical preparation according to claim 1 comprising a step of mixing oxaliplatinum with a solvent comprising a sufficient quantity of at least one hydroxylated derivative selected among 1,2-propanediol, glycerol, maltitol, saccharose and inositol.

11. Method according to claim 10, characterized in that it comprises the following steps:

    a) put in contact at a temperature less than 80°C a quantity of oxaliplatinum with a sufficient quantity of the said solvent to obtain an oxaliplatinum concentration of at least 7 mg/ml;

    b) establish the mixture obtained at the step a) at a temperature comprised between 15-30°C;

    c) submit the mixture obtained at the step b) to an aseptic filtration; and

    d) the conservation in an adapted container for a parenteral administration of the mixture obtained at the step c) at a temperature comprised between 2-30°C.

15. A multidoses flask containing the pharmaceutical preparation according to claim 1.

16. A prefilled syringe containing the pharmaceutical preparation according to claim 1.

17. A soft perfusion bag containing the pharmaceutical preparation according to claim 1.

(IX) EVIDENCE APPENDIX

None – other than the USPTO file history of the subject application.

(X) RELATED PROCEEDINGS APPENDIX

None.